Reproductive and Developmental Toxicity of Polycyclic Aromatic Hydrocarbons (PAHs)

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Introduction

•Polycyclic Aromatic Hydrocarbons (PAHs)

- •PAHs represent a class of organic hydrocarbons, generally with two or more fused aromatic rings containing only carbon and hydrogen atoms and including substituted and alkyl-substituted PAHs
- •PAHs found in air, water and soil and are the products of incomplete combustion and pyrolysis of coal, oil, gas, wood, and other organic substances and are often components of asphalt, crude oil, creosote, coal tar pitch, and roofing tar
- ▪PAHs occur in the environment as complex mixtures

•Rationale for examining the reproductive and developmental effects of PAH exposure

- •An association between prenatal PAH exposure and adverse reproductive and developmental outcomes has been suggested recently in the peer-reviewed literature
- •For example, 9/11/2001 World Trade Center disaster studies and ambient air pollution and PM studies in Poland and Czechoslovakia suggest PAHs may be responsible for adverse effects in exposed fetuses
- •Several studies report that in utero exposures to PAHs lead to intrauterine growth restriction/retardation (IUGR) in humans, but these data are equivocal

•Purpose of the current project : The purpose of the current project was to comprehensively evaluate the literature and determine the state of the science on PAH exposures and reproductive and developmental effects in humans and laboratory animals. Pregnancy outcomes evaluated in humans were: IUGR, birth weight, birth length, head circumference, gestational length, and whether infants were small for gestational age (SGA). DNA adduct data in mothers and newborns potentially exposed to PAHs were also evaluated. Reproductive and developmental effects evaluated in laboratory animals were: birth weight, crown-rump length, breeding success, viable offspring, gonadal weights and morphology, hormone levels, and survival.

Methods

•Literature Search

A search of the peer-reviewed scientific literature was conducted using the following search engines: Medline, Science Direct, Ingenta, Current Contents from 1990 to April 2005

The following search terms were used: PAHs, polycyclic aromatic hydrocarbons, in utero, infant mortality, birth weight, birth length, fetal weight, IUGR, prenatal, postnatal, perinatal, reproductive, developmental, premature, fetal growth, head circumference, body length, gestational duration, gestational length, preterm birth, SGA, fetus, low birth weight

•Definitions Used for Reproductive and Developmental Endpoints

Low birth weight (LBW) - Live birth weighing < 2,500 grams (regardless of gestational age).

Small for gestational age (SGA) - Usually a consequence of IUGR which can be defined as birth weight below the 10th percentile for that gestational age (most widely used definition for SGA); birth weight less than the 3rd percentile for gestational age; or birth weight less than two standard deviations for gestational age. Not all fetuses that are SGA are affected by IUGR, some fetuses may be constitutionally small. Similarly, not all fetuses that have not met their genetic growth potential are in less than the 10th percentile for fetal weight.

Intrauterine growth restriction/retardation (IUGR) - Pathological reduction in an expected pattern of fetal growth that leads the attenuation of fetal growth potential due to an insult that has occurred in utero. Risk factors include maternal nutrition, multiple births, adolescent pregnancies, alcohol and/or substance abuse, inter-pregnancy intervals, high altitude, infections (i.e., rubella, syphilis, herpes, HIV, hepatitis, etc.), metabolic disorders, genetic and chromosomal factors, abnormal placentation and placental insufficiencies (pre-eclampsia and eclampsia), thrombophilia, environmental factors (i.e., cigarette smoke, particulate matter, etc.). Consequences of IUGR include impaired cognitive development, diabetes, obesity, cardiovascular problems, metabolic disorders, and early adolescent development. The most widely used definition of IUGR is a fetus whose estimated weight is below the 10th percentile for its gestational age and whose abdominal circumference is below the 2.5th percentile.

Symmetric IUGR - Fetus develops slowly throughout gestation; affected at a very early stage in pregnancy; proportionate reduction in head circumference, body length, and weight for gestational age.

Asymmetric IUGR - Fetus develops normally throughout the first two trimesters, but growth is affected in the last trimester; body length and weight are decreased for gestational age, but head circumference is proportionate for gestational age.

Summary of Results and Conclusions

•Limitations of the studies evaluated

- •Human studies involve exposure to multiple environmental chemicals in ambient air
- •Reproductive and developmental responses are often weak
- •There is often a misclassification of exposures
- •Observed health effects may have multiple modes of action and etiologies

•Conclusions

- •Studies in humans evaluating the effects of ambient air pollution and/or PAHs provide some evidence to suggest that PAHs may affect the developing fetus
- •Studies do not provide definitive evidence as to whether PAHs or particulate matter alone or in combination are responsible for the developmental effects observed in humans
- •A few studies in experimental animals support the human evidence that PAHs may affect the developing fetus
- •The mode(s) of action by which PAHs affect the development of the fetus is unclear
- •Further studies evaluating PAH exposures and biomarkers of exposures in varied populations of pregnant women and infants are needed
- •Further studies are needed in animal models evaluating different periods of exposure (pre-, peri-, and postnatal); reproductive and developmental endpoints (malformations, gonadal morphology, breeding studies, etc.); and PAHs (mixtures and PAHs other than BaP)

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Recent literature in chronological order describing the reproductive and developmental effects associated with human exposures to PAHs

Study	Study population/Exposure measured	Results and conclusions
Perera et al., 2005; Lederman et al., 2004	Pregnant women (enrolled at the time of labor and delivery) who either resided within 1-2 miles of the World Trade Center (WTC) site; worked, but did not reside within 1-2 miles of the WTC site; or neither resided nor worked within 1-2 miles of the WTC site on and during the month following 9/11/2001.	•Mean maternal and cord blood DNA adduct levels were highest in those residing within 1 mile of the WTC site; intermediate in those working, but not residing within 1 mile of the WTC site; and lowest in the referent group that did not reside nor work within 1 mile of the WTC site. •A significant inverse relationship was observed correlating cord adduct levels in infants born of mothers living within 1 mile of the WTC site on or the month following 9/11/2001 with linear distance from the site. •There were no independent effects of PAH DNA adducts on head circumference, birth weight, or birth length. The presence of adducts in combination with environmental tobacco smoke (ETS) exposure resulted in decreased birth weight (8%) and head circumference (3%). •Women who lived within 2 miles of the WTC site on 9/11/2001 and who were in their first trimester of pregnancy gave birth to babies that were significantly lower in weight and length compared to other pregnant women enrolled in the study. •Pregnant women in their first trimester at the time of the attacks on the WTC (regardless of proximity of residence or employment) had fetuses with decreased gestational length compared to those women at later stages of pregnancy at the time of the attacks.
Bocskay et al., 2005; Perera et al., 2004; Perera et al., 2003	Pregnant Dominican and African American women residing in New York City, NY between 1997 and 2001. Personal air monitoring for two consecutive days during the 3rd trimester of pregnancy. Study designed to examine link between cytogenetic damage and susceptible populations for developing cancer.	•Ambient PAH levels were significantly ($p < 0.01$) associated with chromosomal aberrations in cord blood, but PAH DNA adducts were not associated with cord blood lymphocyte chromosomal aberrations. •BaP DNA adduct levels in maternal and cord blood samples were not significantly correlated with birth outcomes. •A significant reduction in birth weight and head circumference was observed when taking into account both BaP DNA adduct levels and exposure to ETS. •Mean levels of BaP DNA adduct levels were comparable between infant and maternal blood samples. •In infants exposed to PAHs, there was a significant decrement in head circumference and birth weight among African American women, but not Dominican women.
Landrigan et al., 2004	Single live births from pregnant women residing or working near the WTC disaster site in the two weeks following 9/11/2001. U.S. EPA air samples collected at or near the WTC site from September 2001 to May 2002.	•Mean airborne concentrations of PAH mixtures were highest immediately after the disaster then declined over the following weeks. •There was a two-fold increase in the determination of infants that were small for gestational age (SGA). •Gestational duration was significantly shorter in the exposed group. •Particulate matter (PM) and PAHs may be responsible for the fetal effects observed, but an association was not quantified.
Berkowitz et al., 2003	Pregnant women that resided or were employed in or near the WTC disaster site on 9/11/2001 at 9 AM or within the succeeding 3 weeks.	•There was a two-fold increased risk for IUGR in infants born to women in or near the WTC site on or after 9/11/2001 (adjusted odds ratio [OR] = 1.90, 95% confidence interval [CI] 1.058-3.46). •There was no significant difference in the frequency of IUGR according to trimester at the time of exposure to the WTC attacks. •There was no significant association observed between post-traumatic stress disorder and any of the birth outcomes evaluated.
Perera et al., 2002; Perera et al., 1999; Perera et al., 1998	Mother and newborn pairs from Poland enrolled between January and March 1992. Daily ambient air monitoring data from 1991-1992. PM_{10} levels were estimated for each woman by taking the average of measurements at the station closest to her residence during the year preceding her delivery date. BaP levels were also estimated.	•There were elevated PAH and aromatic DNA adduct levels in infants compared to mothers. PAH DNA adducts were not a significant predictor of hypoxanthine-quanine ribosyl transferase in either mothers or infants. •Considering all newborns with high PAH DNA adduct levels collectively, there was a significant decrease in head circumference, birth length, and birth weight ($p \leq 0.03$) compared to infants with lower PAH DNA adduct levels. •PAH levels were inversely related to head circumference both before and after controlling for birth weight ($p < 0.006$ and 0.003, respectively).
Dejmek et al., 2000	All single, full term (≥ 37 weeks) births occurring in two districts in Northern Bohemia from April 1994 to March 1998. Mean $PM_{2.5}$, PM_{10}, and carcinogenic PAHs (c-PAHs) were determined by continuous air monitoring from April 1991 to March 1998. Air levels were determined for nine consecutive 30-day periods.	•A significant association between IUGR risk and PM_{10} levels (medium and high) and PAHs was observed for the first gestational month in the more industrial district. •The association was also observed during the eighth gestational month, although it was only statistically significant at the high level PAH. •Based on the similarities in the association between IUGR and PAHs and PM and the high correlation between PM and PAH levels, the results are not definitive as to whether the developmental effects observed were due to PM, PAHs, or both acting either synergistically or additively.
Gladen et al., 2000	Women (200) delivering babies in two Ukranian cities between November 1993 and December 1994. No specific measures of exposure were reported. Cities were chosen as part of an ongoing assessment of reproductive outcome in areas with limited pollution controls.	•There were no observed effects of PAH exposure on birth outcomes.